Supplemental Data S. Daptomycin Pharmacokinetics in Children Undergoing Hemodialysis and Peritoneal Dialysis: A Case Series With Pharmacokinetic Modeling

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Methods

Monte Carlo Simulations. We performed simulations of concentration-time profile for different regimens based on Monte Carlo methodology using the final population pharmacokinetics (PK) model. We assumed a linear PK for daptomycin in pediatrics, as the PK were linear in young adults at doses up to 12 mg/kg.[1] A 10,000-virtual subjects simulation was conducted for each regimen. The dosing weight was set to the average dry weight (40 kg) of all subjects enrolled. Two cohorts of hemodialysis (HD) daptomycin dosing regimens were simulated: 1) 5, 7, 9, or 12 mg/kg of daptomycin given on Mondays, Wednesdays, and Fridays immediately after HD, 2) identical doses of daptomycin given thrice weekly immediately after HD, with 50% dose increase on Fridays. The infusion time was 30 minutes. The HD duration was scheduled for 3 hours.

The AUC to MIC ratio (AUC/MIC) for 0 to 24 hours, 24 to 48 hours, and, during a 72-hour interdialytic period (Friday through Sunday), 48 to 72 hours after the dose ($AUC_{0–24}$/MIC, $AUC_{24–48}$/MIC, and $AUC_{48–72}$/MIC) were calculated for each virtual subject. In continuous cycling peritoneal dialysis (CCPD) simulations, the dosing schedules were 5, 7, 9, and 12 mg/kg every-48-hour of daptomycin. The CCPD was scheduled during bedtime, with 1.5 L dialysate fluid, 1-hour dwell time for 8 cycles with 15-minute drain/fill period between cycles (first CCPD 14 hours post-daptomycin infusion). After the nighttime treatment, 500 mL of dialysate fluid was added for the 14-hour day dwell. The $AUC_{0–24}$/MIC and $AUC_{24–48}$/MIC after 2 doses of daptomycin were calculated for each CCPD subject. The simulations were conducted in Phoenix NLME.

Pharmacodynamic Target Attainment (PTA) Analysis. The aim was to examine the pharmacodynamic outcome. The daily AUC/MIC ratio of 438 was the pharmacodynamic target that represents the threshold for daptomycin bacteriostatic activity against *Staphylococcus aureus*, as reported by Safdar et al.[1] The target attainment analysis focused on Fridays, Saturdays, and Sundays. The AUC/MIC on Fridays represents the AUC/MIC on Mondays and Wednesdays, whereas the AUC/MIC on Saturdays represents Tuesdays and Thursdays. The AUC/MIC on Sundays were of interest due to concerns about subtherapeutic daptomycin concentrations. Trough concentrations at steady state (prior to dialysis before the third dose for HD subjects and CCPD subjects) above 24.3 mg/L were used as markers for increased risk of toxicity[2–4]; MICs of 0.12, 0.25, 0.5, and 1 mg/L were used. Target attainment rate was calculated by dividing the number of virtual subjects who achieve AUC/MIC >438 by total number of subjects who receive the same dosing regimen. Similarly, the rate of increased risk of toxicity was calculated by dividing the number of virtual subjects who had a trough concentration above 24.3 mg/L by the total number of virtual subjects who receive the same dosing regimen. A priori, dosing regimens with ≥90% target attainment rate were considered efficacious, whereas >10% trough concentrations above 24.3 mg/L were considered unacceptably high risk of toxicity.[2]

Results

Virtual subjects received 3-hour HD thrice weekly (Mondays, Wednesdays, and Fridays), and daptomycin immediately after the completion of each HD to avoid drug loss (Figure 3A). When the MIC ≤0.25 mg/L, all dosing regimens achieved >90% PTA; hence, the lowest safe and effective dose was 5 mg/kg thrice weekly immediately after HD (Table). With a MIC of 0.5 mg/L, only 9 mg/kg resulted in 90% PTA without the increased risk of toxicity. Dosing regimens <9 mg/kg failed to achieve ≥90% PTA during the 72-hour dosing interval between Fridays and the following Mondays (i.e., $AUC_{48–72}$/MIC; Table). Increasing to 12 mg/kg resulted in >50% with elevated trough concentrations. To account for the 72-hour interdialytic period, we evaluated those same doses on Mondays and Wednesdays, but with a 50% higher dose on Fridays. Post-HD 7 mg/kg with 150% on Fridays was the most appropriate regimen for a MIC of 0.5 mg/L, with the PTA >90% at all times and $P_{trough>24.3}$ <1%. No dosing regimen ≤12 mg/kg achieved a PTA >90% for a MIC ≥1 mg/L.

Simulations were conducted for CCPD subjects receiving daptomycin every-48-hours and 8 cycles of 1-hour PD during nighttime, 15-minutes between-cycle drain/fill time, and 14-hours day dwell. The 5 mg/kg every-48-hours regimen achieved bacteriostatic effect with a MIC ≤0.25 mg/L. With a MIC of 0.5 mg/L, all subjects achieved target with ≥7 mg/kg daptomycin. When the MIC was 1 mg/L, 12 mg/kg was needed.

Table. Probability of Pharmacodynamic Target Attainment (PTA; %)*

	AUC/MIC (MIC = 0.12)			AUC/MIC (MIC = 0.25)			AUC/MIC (MIC = 0.5)			AUC/MIC (MIC = 1)			Trough
	0–24 hr	24–48 hr	48–72 hr	0–24 hr	24–48 hr	48–72 hr	0–24 hr	24–48 hr	48–72 hr	0–24 hr	24–48 hr	48–72 hr	>24.3 mg/L
Post-HD													
5 mg/kg	100	100	100	100	100	95	100	99	6.8	100	3.7	0	0
7 mg/kg	100	100	100	100	100	100	100	100	56	100	62	0	<1
9 mg/kg	100	100	100	100	100	100	100	100	90	100	97	2.1	5.9
12 mg/kg	100	100	100	100	100	100	100	100	99	100	100	28	51
5 mg/kg (150% F)	100	100	100	100	100	100	100	100	58	100	64	< 1	0
7 mg/kg (150% F)	100	100	100	100	100	100	100	100	96	100	99	5.7	<1
9 mg/kg (150% F)	100	100	100	100	100	100	100	100	100	100	100	38	6.3
12 mg/kg (150% F)	100	100	100	100	100	100	100	100	100	100	100	85	52
PD													
5 mg/kg	100	100		100	100		100	84		100	<1		0
7 mg/kg	100	100		100	100		100	100		100	16		0
9 mg/kg	100	100		100	100		100	100		100	66		<1
12 mg/kg	100	100		100	100		100	100		100	97		1.8

* Probabilty of achieving PTA AUC/MIC > bacteriostatic level (438) during a 72-hr intradialytic period (i.e., Fridays [0–24 hr], Saturdays [24–48 hr], Sundays [48–72 hr]) is based on thrice weekly (Monday-Wednesday-Friday) hemodialysis (HD) regimens (post-HD dosing and post-HD with 150% Friday dose [150% F]), and PTA of every-48-hour dosing for continuous cycling peritoneal dialysis (CCPD), and the rate of high toxicity risk (trough level < 24.3 mg/L). Cells coded with no color represent >90% PTA and with light gray color represent <90% PTA of virtual subjects. Dark gray coding represents >10% of virtual subjects with a trough concentration exceeding 24.3 mg/L.

References

1. Safdar N, Andes D, Craig WA. In vivo pharmacodynamic activity of daptomycin. *Antimicrob Agents Chemother*. 2004;48(1):63–68.
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